Complete Summary

GUIDELINE TITLE

Disorders of sex development. In: Guidelines on paediatric urology.

BIBLIOGRAPHIC SOURCE(S)

Disorders of sex development. In: Tekgul S, Riedmiller H, Gerharz E, Hoebeke P, Kocvara R, Nijman R, Radmayr C, Stein R. Guidelines on paediatric urology. Arnhem, The Netherlands: European Association of Urology, European Society for Paediatric Urology; 2008 Mar. p. 67-72. [15 references]

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Disorders of sex development (formerly known as intersex disorders, pseudohermaphroditism, hermaphroditism)

Note: Disorders of sex development includes congenital conditions with atypical development of chromosomal, gonadal or anatomical sex.

GUIDELINE CATEGORY

Counseling
Diagnosis
Evaluation

Management
Treatment

CLINICAL SPECIALTY

Endocrinology
Medical Genetics
Obstetrics and Gynecology
Pediatrics
Psychology
Surgery
Urology

INTENDED USERS

Allied Health Personnel
Physicians
Psychologists/Non-physician Behavioral Health Clinicians
Social Workers

GUIDELINE OBJECTIVE(S)

- To outline a practical and preliminary approach to paediatric urological problems
- To increase the quality of care for children with urological problems

TARGET POPULATION

Children and adolescents from birth to puberty who are born with disorders of sex development

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Evaluation

1. Early recognition of disorders of sexual development (DSD)
2. Family history and thorough clinical examination
3. Laboratory investigations
    - Karyotyping
    - Plasma-17-hydroyprogesterone assay
    - Plasma electrolytes
    - Ultrasonography to evaluate the present of Müllerian duct structures
    - Human chorionic gonadotrophin (hCG) stimulation test
    - Genitography
    - Androgen-binding studies
    - Cystoscopy
    - Diagnostic laparoscopy

Treatment/Management

1. Making gender assignment decisions

2. Timing of surgery
    - Feminizing surgery: clitororeduction, separation of the vagina and urethra, vaginoplasty, aesthetic refinements
    - Masculinizing surgery: hypospadias surgery, excision of Müllerian structures, orchiopexy, phalloplasty, aesthetic refinements, gonadectomy
3. Hormone therapy

MAJOR OUTCOMES CONSIDERED

Sexual functioning

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guidelines were based on current literature following a systematic review using MEDLINE.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

1a Evidence obtained from meta-analysis of randomized trials

1b Evidence obtained from at least one randomized trial

2a Evidence obtained from at least one well-designed controlled study without randomization

2b Evidence obtained from at least one other type of well-designed quasi-experimental study

3 Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports

4 Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Application of a structured analysis of the literature was not possible due to a lack of well-designed studies. Whenever possible, statements have been classified in terms of level of evidence and grade of recommendation. Due to the limited availability of large randomized controlled trials – influenced also by the fact that a considerable number of treatment options relate to surgical interventions on a large spectrum of different congenital problems – this document is therefore largely a consensus document.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

- The first step in the European Association of Urology (EAU) guidelines procedure is to define the main topic.
- The second step is to establish a working group. The working groups comprise about 4-8 members, from several countries. Most of the working group members are academic urologists with a special interest in the topic. In general, general practitioners or patient representatives are not part of the working groups. A chairman leads each group. A collaborative working group consisting of members representing the European Society for Paediatric Urology (ESPU) and the EAU has gathered in an effort to produce the current update of the paediatric urology guidelines.
- The third step is to collect and evaluate the underlying evidence from the published literature.
- The fourth step is to structure and present the information. The strength of the recommendation is clearly marked in three grades (A-C), depending on the evidence source upon which the recommendation is based. Every possible effort is made to make the linkage between the level of evidence and grade of recommendation as transparent as possible.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grades of Recommendation

A. Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial
B. Based on well-conducted clinical studies, but without randomized clinical studies
C. Made despite the absence of directly applicable clinical studies of good quality

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

There is no formal external review prior to publication.

The Appraisal of Guidelines for Research and Evaluation (AGREE) instrument was used to analyse and assess a range of specific attributes contributing to the validity of a specific clinical guideline.

The AGREE instrument, to be used by two to four appraisers, was developed by the AGREE collaboration (www.agreecollaboration.org) using referenced sources for the evaluation of specific guidelines. (See the "Availability of Companion Documents" field for further methodology information).

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Levels of evidence (**1a-4**) and grades of recommendation (**A-C**) are defined at the end of the "Major Recommendations" field.

Background

The formerly called 'intersex disorders' were recently the subject of a consensus document in which it was decided that the term 'intersex' should be changed to 'disorders of sex development' (DSD).

DSD require a multidisciplinary approach to diagnosis and treatment, which should include geneticists, neonatologists, paediatric and adult endocrinologists, gynaecologists, psychologists, ethicists and social workers. Each team member should be specialised in DSD, and a team should have enough new patients to ensure experience.

The Neonatal Emergency

The first step is to recognize the possibility of DSD (see Table 4 in the original guideline document) and to refer the newborn baby immediately to a tertiary paediatric centre, fully equipped with neonatal, genetics, endocrinology and paediatric urology units. At the paediatric centre, the situation should be explained to the parents fully and kindly. Registering and naming the newborn should be delayed as long as necessary.

Choice of Laboratory Investigations

The following laboratory investigations are mandatory:

- Karyotype
- Plasma 17-hydroxyprogesterone assay
- Plasma electrolytes
- Ultrasonography to evaluate the presence of Müllerian duct structures

These investigations will provide evidence of congential adrenal hyperplasia (CAH), which is the most frequently occurring DSD. If this evidence is found, no further investigation is needed. If not, then the laboratory work-up should proceed further.

The human chorionic gonadotrophin (hCG) stimulation test is particularly helpful in differentiating the main syndromes of 46XYDSD by evaluating Leydig cell potential. When testosterone metabolism is evaluated, the presence or absence of metabolites will help to define the problem. An extended stimulation can help to define phallic growth potential and to induce testicular descent in some cases of associated cryptorchidism.

Gender Assignment

This is a very complicated task. It should take place after a definitive diagnosis has been made. The idea that an individual is sex-neutral at birth and that rearing determines gender development is no longer the standard approach. Instead, gender assignment decisions should be based upon:

- Age at presentation
- Fertility potential
- Size of the penis
- Presence of a functional vagina
- Endocrine function
- Malignancy potential
- Antenatal testosterone exposure
- General appearance
- Psychosocial well-being and a stable gender identity

Each patient presenting with DSD should be assigned a gender as quickly as a thorough diagnostic evaluation permits.

Role of the Paediatric Urologist

The role of the paediatric urologist can be divided into a diagnostic role and a therapeutic role (see Table below).

Table. Role of the Paediatric Urologist

Diagnostic role

• Clinical examination • Ultrasound • Genitography • Cystoscopy • Diagnostic laparoscopy
Therapeutic role • Masculinizing surgery • Feminizing surgery • Gonadectomy

Diagnosis

Clinical Examination

A good clinical examination in a neonate presenting with ambiguous genitalia is important. As well as a good description of the ambiguous genitalia, some detailed information should be given on palpability and localization of the gonads. Information gathered by the various examinations described below should help the team to come to a final diagnosis.

Palpable gonad. It must be remembered that if it is possible to feel a gonad, it is almost certainly a testis; this clinical finding therefore virtually excludes 46XXDSD.

Medical photography can be useful but requires sensitivity and consent.

Phallus. The phallus should be measured. A cotton bud placed at the suprapubic base of the implant of the stretched phallus allows for a good measurement of phallic length.

Urogenital sinus opening. The opening of the urogenital sinus must be well evaluated. Is there only one opening visible? Can a hymenal ring be seen? What does the fusion of the labioscrotal folds look like; do the folds show rugae or some discolouration?

Investigations

Ultrasound can help to describe the palpated gonads or to detect non-palpated gonads. However, the sensitivity and specificity are not high. On ultrasound, the Müllerian structures can be evaluated. Is there a vagina? Are there some abdominal gonads? Is there a vaginal or utricular structure visible?

Genitography can provide some more information on the urogenital sinus. How low or how high is the confluence? Is there any duplication of the vagina? How does the urethra relate to the vagina?

General anaesthesia. In some cases, further examinations under general anaesthesia can be helpful. On cystoscopy, the urogenital sinus can be evaluated and the level of confluence between the bladder neck and the bladder. Cystoscopy can also be used to evaluate the vagina or utriculus, e.g., the presence of a cervix at the top of the vagina can be important information.

Laparoscopy is necessary to obtain a final diagnosis on the presence of impalpable gonads and on the presence of Müllerian structures. If indicated, a gonadal biopsy can be performed.

Management

It is clear that the timing of surgery is much more controversial than it used to be.

The rationale for early surgery includes:

- Beneficial effects of oestrogen on infant tissue
- Avoiding complications from anatomical anomalies
- Minimizing family distress
- Mitigating the risks of stigmatization and gender-identity confusion

However, adverse outcomes have led to recommendations to delay unnecessary surgery to an age when the patient can give informed consent. Surgery that alters appearance is not urgent. Early surgery should be reserved for those patients with high confluent urogenital tracts, girls with severely masculinized genitalia and boys with undervirilized genitals. Vaginoplasty should be delayed until puberty and milder forms of masculinization should not be treated surgically.

Feminizing Surgery

Clitororeduction. Reduction of an enlarged clitoris should be done with preservation of the neurovascular bundle. Clitoral surgery has been reported to have an adverse outcome on sexual function and clitoral surgery should therefore be limited to severely enlarged clitorises. Informed parental consent should be obtained. Although some techniques that conserve erectile tissue have been described, the long-term outcome is unknown.

Separation of the vagina and the urethra is preserved for high confluence anomalies. Many techniques for urogenital sinus repair have been described, but their outcome has not been evaluated prospectively.

Vaginoplasty should be performed during the teenage years. Every technique (self dilatation, skin or bowel substitution) has its specific advantages and disadvantages. All carry a potential for scarring that would require further surgery before sexual function was possible.

Aesthetic refinements. The goals of genital surgery are to maximize anatomy to allow sexual function and romantic partnering. Aesthetics are important in this perspective. The reconstruction of minor labiae from an enlarged clitoral hood is an example of aesthetic refinement.

Masculinizing Surgery

Hormone therapy early in life is advocated by many doctors. The level of evidence is low for restoration of normal penile size.

Hypospadias surgery. See the National Guideline Clearinghouse (NGC) summary of the EAU guideline, Hypospadias.

Excision of Müllerian structures. In the DSD patient assigned a male gender, Müllerian structures should be excised. There is no evidence about whether utricular cysts need to be excised.

Orchiopexy. See the NGC summary of the EAU guideline, Cryptorchidism.

Phalloplasty. The increasing experience of phalloplasty in the treatment of female to male transsexual patients has led to reports about the reliability and feasibility of this technique. It has therefore become available to treat severe penile inadequacy in DSD patients.

Aesthetic refinements. These include correction of penoscrotal transposition, scrotoplasty and insertion of testicular prostheses.

Gonadectomy. Germ cell malignancy only occurs in patients with DSD who have Y-chromosomal material. The highest risk is seen in patients with gonadal dysgenesis and in patients with partial androgen insensitivity with intra-abdominal gonads (**Level of evidence: 2**). Intra-abdominal gonads of high-risk patients should be removed at the time of diagnosis (**Grade of recommendation: A**).

Definitions:

Levels of Evidence

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Grades of Recommendation

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CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Overall, there is a low evidence base for the published literature on disorders of sex development. There are no randomized controlled trials and most studies are based on retrospective clinical descriptive studies (grade 4 level of evidence) or are expert opinion. An exception is the risk of gonadal cancer, for which the level of evidence is higher (see "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate and timely diagnosis, treatment, and management of neonates with disorders of sex development

POTENTIAL HARMS

All types of vaginoplasty carry a potential for scarring that would require further surgery before sexual function is possible.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

The purpose of these texts is not to be proscriptive in the way a clinician should treat a patient but rather to provide access to the best contemporaneous consensus view on the most appropriate management currently available. European Association of Urology (EAU) guidelines are not meant to be legal documents but are produced with the ultimate aim to help urologists with their day-to-day practice.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The European Association of Urology (EAU) Guidelines long version (containing all 19 guidelines) is reprinted annually in one book. Each text is dated. This means

that if the latest edition of the book is read, one will know that this is the most updated version available. The same text is also made available on a CD (with hyperlinks to PubMed for most references) and posted on the EAU websites Uroweb and Urosource (www.uroweb.org/professional-resources/guidelines/ & http://www.urosource.com/diseases/).

Condensed pocket versions, containing mainly flow-charts and summaries, are also printed annually. All these publications are distributed free of charge to all (more than 10,000) members of the Association. Abridged versions of the guidelines are published in European Urology as original papers. Furthermore, many important websites list links to the relevant EAU guidelines sections on the association websites and all, or individual, guidelines have been translated to some 15 languages.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness
Timeliness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Disorders of sex development. In: Tekgul S, Riedmiller H, Gerharz E, Hoebeke P, Kocvara R, Nijman R, Radmayr C, Stein R. Guidelines on paediatric urology. Arnhem, The Netherlands: European Association of Urology, European Society for Paediatric Urology; 2008 Mar. p. 67-72. [15 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2008 Mar

GUIDELINE DEVELOPER(S)

European Association of Urology - Medical Specialty Society
European Society for Paediatric Urology - Medical Specialty Society

SOURCE(S) OF FUNDING

European Association of Urology

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Authors: S. Tekgül; H. Riedmiller; E. Gerharz; P. Hoebeke; R. Kocvara; R. Nijman; Chr. Radmayr; R. Stein

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

All members of the working group submit a conflict of interest form. The information is kept on file in the European Association of Urology (EAU) Central Office database. This guidelines document was developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance, travel, and meeting expenses. No honoraria or other reimbursements have been provided.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the European Association of Urology Web site.

Print copies: Available from the European Association of Urology, PO Box 30016, NL-6803, AA ARNHEM, The Netherlands.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- EAU guidelines office template. Arnhem, The Netherlands: European Association of Urology (EAU); 2007. 4 p.
- The European Association of Urology (EAU) guidelines methodology: a critical evaluation. Arnhem, The Netherlands: European Association of Urology (EAU); 18 p.

Print copies: Available from the European Association of Urology, PO Box 30016, NL-6803, AA ARNHEM, The Netherlands.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI Institute on November 18, 2008. The information was verified by the guideline developer on December 19, 2008.

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